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The Congenital Syphilis Prevention Cascade: Reimagining a Missed Prevention Opportunities Framework for Effective Intervention

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Abstract

Congenital syphilis (CS) rates have risen in the United States since 2013. Prevention of CS requires testing and treatment of pregnant and pregnancy-capable persons at high risk for syphilis. We developed a CS Prevention Cascade to assess how effectively testing and treatment interventions reached pregnant persons with a CS outcome.

Rates of congenital syphilis (CS) have risen in the United States since 2013.¹ Although CS is an avoidable outcome if a pregnant person with syphilis receives appropriate testing and treatment at least 30 days before delivery, approximately one-fourth of pregnancies affected by syphilis result in a CS outcome (ie, a livebirth or stillbirth affected by CS).² National surveillance data have been used to identify missed opportunities for CS prevention, primarily by addressing timeliness of prenatal care, as well as timeliness of testing and treatment Supplementary Fig. 1, <http://links.lww.com/OLQ/A998>.^{1,3} This framework requires prenatal services as an entry point to the cascade. This restricts our understanding of persons who may not receive prenatal care but do receive testing and treatment, an important limitation as the continued rise in rates of CS necessitates additional resources, including testing and treatment for pregnant persons in settings outside of traditional prenatal care.^{4,5} As we work to develop new strategies to curb the growing epidemic of CS, we sought to clarify and organize elements of the current framework for missed prevention opportunities into a primary prevention cascade focused on successful testing and treatment. The goal of

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this work is to allow us to better describe regional and local targets for intervention with tangible goals, as well as account for a shifting health care landscape in the context of a rapidly growing epidemic. This landscape includes the increasing receipt of elements of prenatal care in nontraditional venues of care such as emergency departments and substance use disorder treatment settings, as well as the merging syndemics of syphilis and substance use.⁵

METHODS

Data Sources

We extracted CS case data for the year 2021 from the National Notifiable Diseases Surveillance System (NNDSS) for all 50 states, the District of Columbia, and US Territories and Freely Associated States (reported as of June 24, 2023). Syphilis case report data are deidentified, line-listed data which include, among other elements, demographic data and syphilis staging, testing and treatment information for the birthing parent; infant clinical and testing data; and case classification status (syphilitic stillbirth, confirmed case [with positive direct detection tests], or probable case [based on infant/maternal criteria]).⁶ CS case notifications sent to the US Centers for Disease Control and Prevention (CDC) via NNDSS are defined by the Council of State and Territorial Epidemiologists (CSTE) surveillance case definition⁶

Development of a Congenital Syphilis Prevention Cascade

Using NNDSS CS case notification data, we developed a stepwise analytic framework to retrospectively assess the proportion of cases for which the pregnant person had received timely testing and adequate treatment for syphilis during pregnancy Supplementary Fig. 2, <http://links.lww.com/OLQ/A998>. *Testing:* For each case, we assessed whether testing was received and whether the test was timely for the purposes of primary prevention of CS. Sensitivity analyses were performed for both elements to detect the impact of more restrictive definitions of receipt and timeliness of testing Supplementary Table 1, and Supplementary Table 2, <http://links.lww.com/OLQ/A998>. All cases were assigned to either having received (1) timely test, (2) nontimely or nondocumented test, or (3) were identified as having seroconverted late in pregnancy after having a timely nonreactive test earlier in pregnancy.

Treatment—For those cases with a documented timely test, we further assessed whether this test was acted upon with the appropriate treatment for syphilis, based on the documented regimen received by the pregnant person, their reported surveillance stage of syphilis, and the timing of the first dose received relative to the delivery date. Cases with documented evidence of timely testing advance to the treatment section of the cascade, and were assigned to (1) adequate treatment, (2) inadequate treatment (ie, a nonpenicillin regimen, or a regimen not appropriate for stage, not correctly dosed or spaced, or not started until <30 days before delivery), or (3) no or nondocumented treatment. Of note, although persons who received a nontimely test or who were identified to have late seroconversion during pregnancy were not included in the analysis for the treatment stage of this cascade, the 2021 CDC Sexually Transmitted Infection Treatment Guidelines strongly recommend

that all such individuals receive appropriate treatment for their stage of syphilis at the earliest possible opportunity, even if such treatment is considered potentially insufficient for primary prevention of CS.⁷

Outcomes—Lastly, for cases with documented receipt of both a timely test during pregnancy and receipt of a treatment regimen considered effective for primary prevention of CS, we analyzed their subsequent indication for notification as a case of CS based on CSTE's surveillance case definition. Cases in the outcome phase were assigned to either having clinical evidence of CS despite adequate therapy in the birthing parent (if a declarative infant finding was reported), or to missing or nondocumented indication (if no clear indication for inclusion as a reportable case of CS was found).

RESULTS

In the United States in 2021, 2876 cases of CS were notified to CDC through NNDSS, including 198 stillbirths, 14 confirmed cases, and 2664 probable cases. Of all cases, 1513 (52.6%) received a timely test during pregnancy (Fig. 1). A further 175 (6.1%) were identified to have seroconversion late in pregnancy after having had a nonreactive test earlier in pregnancy. A total of 1188 (41.3%) had no documented test or a nontimely test. Of the 1513 who received timely testing, 1284 (84.9%) also had at least one prenatal care visit, while among the 1188 who received no or nontimely testing, 344 (28.9%) had at least one prenatal care visit Supplementary Table 3, <http://links.lww.com/OLQ/A998>.

Of the 1513 cases in receipt of a timely test, 169 (11.2%) received adequate treatment within pregnancy, while a further 986 (65.2%) received inadequate treatment (due to treatment being started less than 30 days before delivery, a nonpenicillin regimen, or a regimen inappropriate for the stage of syphilis). The remaining 358 (23.7%) had no or nondocumented treatment.

Of the 169 cases in birthing parents who received adequate treatment, 93 (55%) of these infants had clinical evidence of CS despite this adequate therapy—32 (34%) with clinical signs or symptoms on examination (regardless of other findings), and 61 (66%) who were well-appearing but had radiographic changes on long bones, positive cerebrospinal fluid [CSF] VDRL testing, or elevated CSF white blood cell count or protein levels. The remaining 76 (45%) were missing data which would have allowed a determination of their indication for being notified as a case. We performed sensitivity analyses assessing the impact of permissive versus restrictive interpretation of timeliness of testing, which displayed minimal impact on case allocation Supplementary Table 1, and Supplementary Table 2, <http://links.lww.com/OLQ/A998>. In this context, we maintained the precedent of considering as timely all tests performed 30 or more days before delivery. Although such tests may have turnaround times associated with limited or no time for adequate treatment, increasing use of rapid tests represents a countervailing pressure, which could lead to misattribution in the opposite direction. As such, maintaining the current 30-day timeliness window likely provides the best balance of accurate case assignment.

DISCUSSION

This novel CS primary prevention cascade illustrates the steps required to avert a potential case of CS, and further demonstrates that in cases which are notified as probable or confirmed CS, some or all of these steps may have been achieved, despite the outcome. In 2021, the 2 most significant primary missed opportunities for CS prevention were either no or nontimely testing (1188 [41.3%]) or no or inadequate treatment (1344 [46.7%]) Supplementary Table 4, <http://links.lww.com/OLQ/A998>.

In restructuring this framework, we sought to highlight specific interventions in the prevention cascade, such as timely testing and adequate treatment, and highlight successes and opportunities in their provision. Further, we sought to provide clarity as to the burgeoning role played by nonprenatal care providers (eg, emergency departments, nonobstetric primary care, public health clinics, etc.) in providing alternate venues for syphilis testing and treatment for pregnant and pregnancy-capable persons of reproductive age, as well as highlight the continued role of prenatal services and prenatal clinical providers in the context of the broader epidemic.

Limitations

Ideally, a prevention cascade such as this would analyze data from all pregnant persons with the exposure in question (syphilis in pregnancy) and follow through to an outcome of either confirmed case, probable case, or case averted. Because of the lack of linkage of birthing parent and infant data in NNDSS, we cannot include data related to the treatment cascade experienced by pregnant persons whose pregnancy outcomes are not surveilled as cases of CS, precluding us from drawing conclusions about differences between these groups. This analysis, although providing a comprehensive national overview, also does not address variations, which may occur in testing and treatment across the spectrum of geography, race, and ethnicity. As such, further work is needed to better elucidate these potential inequities.

CONCLUSION

As the syphilis epidemic continues to grow at an alarming rate among populations of reproductive aged persons, novel approaches are required to better engage those populations with syphilis testing and treatment in a multitude of clinical and nonclinical settings. In addition, a better understanding of current successes and opportunities for improvement, particularly around the provision of timely testing and adequate treatment, remains key to improving public health interventions to turn the tide of this epidemic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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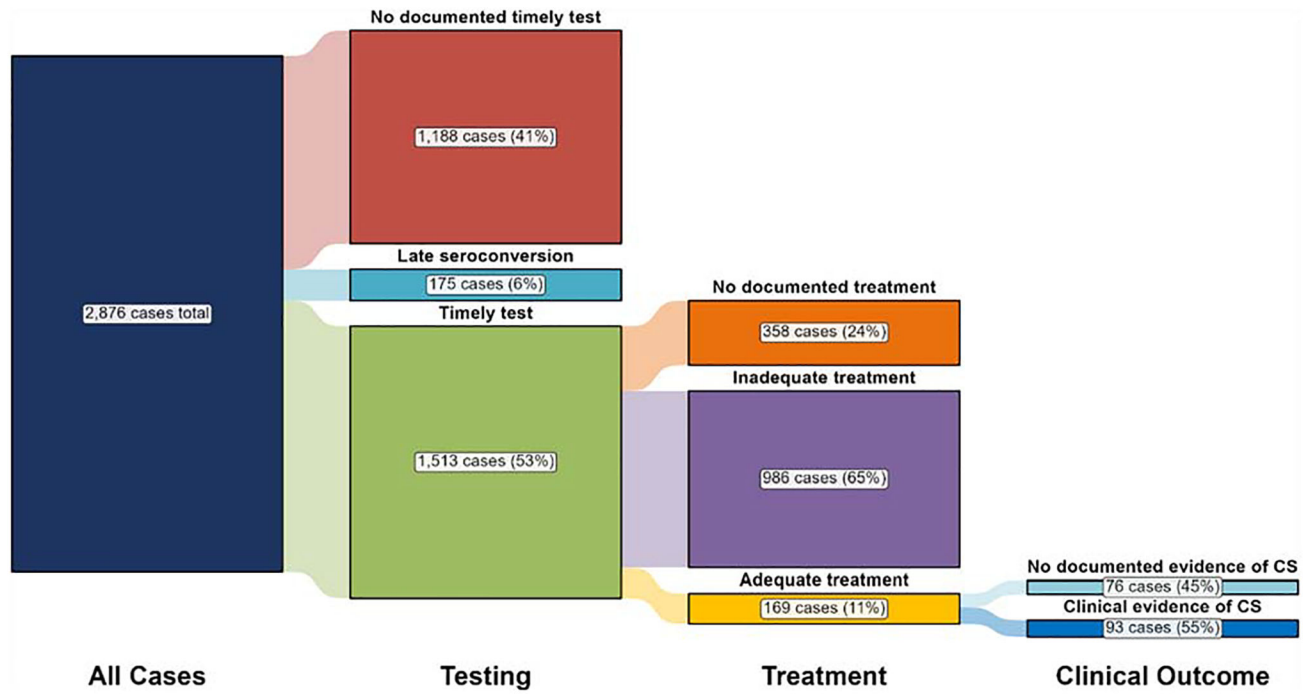


Figure 1. Distribution of receipt of testing and treatment by pregnant persons with a CS outcome, United States, 2021.